REMARKS

Claims 65-82 are pending in the application. By the foregoing amendment claims 67-69 and 76-79 have been cancelled without prejudice or disclaimer. Applicant expressly reserves the right to file a divisional application to pursue the claims cancelled herein. Claims 65, 70, 71, 74, 75, and 82, have been amended. New claim 83, which depends from claim 72, recites that a monovalent antibody fragment includes a variable region having a sequence having at least 80% sequence identity with SEQ IDNO:4 within the CDR region identified in Figure 13. Support for this amendment is found for example at pages 7 (lines 12-13), pages 9 (line 26) to page 10 (line 2), and on page 9 (line 33). No new matter is added. Entry of these amendments is believed to be appropriate and is respectfully requested.

The specification was objected to under 37 C.F.R. § 1.821(d) as failing to provide select sequence identifiers. Claims 65-71, 75, and 80-82 were rejected under 35 U.S.C. § 112, second paragraph. Claims 65-82 were rejected under 35 U.S.C. § 112, first paragraph. Claims 65-70, 72-74, and 76-79 were rejected under 35 U.S.C. § 102(b). And claims 65-70, 72-74, and 76-79 were rejected under 35 U.S.C. § 103(a). Each of these issues is addressed as follows.

Objection under 37 CFR § 1.821(d)

The Office has objected to Applicants' specification under 37 C.F.R. § 1.821(d) as failing to provide a sequence identifier for each individual sequence. To address this issue, Applicants have amended the specification to include sequence identifiers for sequences found on page 27 (lines 21-25) and page 28 (lines 14-15). A revised copy of the sequence listing is enclosed herewith in paper and electronic format.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 65-71, 75, and 80-82 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 71 and 75 have been amended, and now refer to the correct antecedent basis in claims 65 and 72, respectively. Claim 82 has been amended to refer to the monoclonal antibody of claim 80. Claim 65, as amended, now also refers to the presence of a pharmaceutically acceptable carrier in the composition. Support for pharmaceutical compositions comprising both an antibody fragment and a pharmaceutically acceptable carrier can be found throughout the description, more particularly on page 11 lines 22 to 25 of the published PCT application (WO 01/10911). This rejection may now be withdrawn.

Rejections under 35 U.S.C.§ 112, first paragraph

New matter

Claims 65-79 were rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. For the following reasons, this rejection should be withdrawn.

Claims 65 and 72

As an initial matter, Applicants note that monovalent antibody fragments in general were described in the application, at the time of filing, at least on page 6, line 30. In addition, page 14, lines 15-23 further discloses the production of monovalent antibody fragments.

Claims 66 and 73

Support for the specific inclusion of 'single variable domain' is found in the specification as a whole and more particularly on page 1, line 6 which explicitly cites 'single variable domains' as envisaged within the context of the invention. Moreover, it is submitted that claims 24 and 25 of the application as filed, relating to the amino acid

sequences of the single variable domain of the heavy chain and the light chain respectively, further provide support for the fact that the inventors were in possession of single variable domains upon filing the application.

Claim 74

Without acquiescence to the Examiner's objections, claim 74 has been amended to recite adhesion of the platelet at high shear rate. Support for this language is found, for example, on page 17, lines 24 to 27 and page 18, lines 14 to 18, as well as in Figure 2.

Claims 67-70 and 76-79

Claims 67-69 and 76-79 have been cancelled. Claim 70 has been amended to refer to a sequence having at least 80% sequence identity within the CDR region in SEQ ID NO: 4, whereby reference is made to Figure 13. Further support for this amendment is found, for example, on page 7, lines 12-13, which indicates that the invention also envisages homologs of the antigen-binding Fab fragments, and to page 9, line 26 to page 10, line 2, which provides the definition of a homolog and indicates, more particularly, on page 9, line 32 which indicates that "where the ligands of the invention include amino acid sequences" homologies starting from 60% are envisaged. Applicants note that these claims include modifications which occur outside the complementarity determining regions or CDRs. Moreover, that the exact sequence of the framework regions are of minor importance was recognized by Applicants, as stated in the section spanning from page 28, line 33 to page 29, line 2: "...uncertainties in the framework regions are unlikely to affect antigen specificity since this is determined by the complementarity determining regions."

Enablement – Hybridoma Deposit

Applicants note that hybridoma LMBP5108CB was deposited under the terms of the Budapest Treaty as identified on the receipt of the Belgian Coordinated Collections of Microorganisms (BCCM™), which was included in the application as filed and in the

published application on pages 31 and 32. This description clearly provides the accession number for the deposit, the date of the deposit, a description of the deposited biological material, and the name and address of the depository. It is therefore submitted that page 31 clearly indicates the accession number (LMBP 5108CB), and that page 32 indicates that the date of the original deposit to be August 5, 1999 and also provides the address of the International Depository Authority. A description of LMBP 5108CB is found in the specification, for example, on page 7, lines 3-5. Nevertheless, to advance prosecution, Applicants enclose a statement by an inventor, Dr. Hans Deckmyn, with regard to the term of this deposit.

Enablement – Pharmaceutical Compositions

The standard for enablement is articulated in *In re Wands* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In defining the boundaries of undue experimentation, the *Wands* court stated that "the key word is 'undue' not 'experimentation'" and that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *Id.* at 737.

Practitioners of the monoclonal antibody art described in *Wands*, who screened many hybridomas to isolate the one having the desired characteristics, are prepared to screen many antibody molecules to find one that contains a desired property. Such screening of molecules falling within Applicants' claims is considered to be a routine step in the process of isolating molecules having the desired characteristics; it cannot constitute undue experimentation.

As the case of *In re Wands* makes clear, enablement is not negated by the necessity for some experimentation such as routine screening. The present invention, like *In re Wands*, involves screening. As stated *In re Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed." In light of the teaching of the specification, screening antibodies having the required percent identity falling within Applicants' claims might be laborious, but it would not require undue experimentation.

Addressing the Wands factors individually, Applicants note that there is a high level of skill in the art, and the methods needed to practice the invention are available and well known to those skilled in the art. The disclosure provides considerable guidance and includes sufficient working examples to allow one skilled in the art to practice the present invention. Practitioners in the art are prepared to screen many putative antibodies in order to identify those antibodies having the desired characteristics. Moreover, an *in vivo* assay described in the specification can readily be used by one skilled in the art to determine whether a monovalent antibody fragment binds to GP1b or whether a monovalent antibody fragment binds to GP1b and prevents the binding of von Willebrand factor to GP1b. Other routine methods for determining whether an antibody possesses the required features were known in the art at the time of the invention. None of these aforementioned methods constitute undue experimentation. Furthermore, Applicants' examples actually demonstrate that the practice of this invention successfully identifies antibodies having the desired characteristics. Applicants' specification has provided sufficient guidance and data to support the scope of the requested claims. Accordingly, the disclosure satisfies the standard set forth *In re Wands*. The enablement rejection on this basis alone may be withdrawn.

In addition, the Office has indicated that there is insufficient guidance as to what anti-GP1b antibody would lead to inhibition of platelet adhesion under high shear conditions. Applicants note that it is known from the prior art that inhibition of GP1b inhibits platelet aggregation and adhesion. However, the prior art anti-GP1b antibody preparations have been described to induce thrombocytopenia and, therefore, were not considered suitable as pharmaceutical compositions. In contrast, Applicants' claimed pharmaceutical compositions relate to monovalent antibodies against GP1b which, by

virtue of the fact that they monovalent, do not induce thrombocytopenia. Accordingly, any antibody which binds to GP1b is useful for obtaining monovalent antibody fragments having the claimed features.

As evidence of this assertion, the Examiner's attention is directed to the accompanying Declaration of Dr. Hans Deckmym, which provides data relating to a second monovalent antibody fragment that binds to GP1b. As further noted by Dr. Deckmym, contrary to the complete antibody, monovalent antibody fragments of an anti-GP1b antibody do not induce thrombocytopenia *in vivo*.

Furthermore, the Office has indicated that Applicants' specification does not provide reasonable enablement for a composition comprising a monovalent antibody fragment comprising a variable region encoded by a sequence comprising 'any sequence having at least 60% sequence identity' with SEQ ID NO: 1 or 2 (claims 67-68) or a monovalent antibody which inhibits platelet adhesion and/or aggregation under high shear conditions (claim 74).

To expedite prosecution, claims 67-69 and 76-79 have been cancelled. It is, nonetheless, clear that the invention pertains to antibody fragments which are defined in the first instance by their binding affinity to GP1b. With regard to particular embodiments of the invention, such as monovalent GP1b antibody fragments, only the amino acid sequence of the variable domains, and more particularly the CDR regions therein are critical and thus the exact nucleotide sequence which encode these variable domains is not critical.

Moreover, Applicants note that amended claim 70 and new claim 83 each refer to antibody fragments comprising amino acid sequences corresponding a sequence having at least 80% sequence identity within the CDR regions in SEQ ID NO: 4. It should be kept in mind that the invention refers generally to compositions comprising monovalent fragments of antibodies which bind to GP1b. A number of GP1b-binding antibodies are known in the art and can be used to derive the monovalent antibody fragment of the

present invention. Methods to obtain monovalent fragments from antibodies are known in the art and are further detailed, for example, on page 14, lines 15-23.

With regard to the 6B4 antibody, the claims as presently amended now relate to monovalent antibody fragments which bind to GP1b, including variable regions which are at most 20% different within the CDR regions of SEQ ID NO:3 and 4, respectively. In view of the length of the CDR sequences, 27 and 35 amino acids respectively, a 20% difference corresponds to about 5-7 amino acids where differences may occur. It is again submitted that it is certainly within the skill of the scientist working in the field of antibodies to modify an antibody in the regions outside the CDRs, while ensuring that antigen specificity is not affected. Similarly, it cannot be considered undue burden for the skilled person to make limited modifications within the CDRs identified in Figure 14, to obtain a monovalent antibody fragment derived from antibody 6B4 which is equally capable of binding GPIb. This is because the binding of the antibody to GP1b can easily be ascertained.

With regard to claim 74, this claim has now been amended to refer only to platelet adhesion, which can be tested as described on page 17, lines 24 to page 18 line 4 of the application as filed.

As indicated above however, it should be noted that the present invention is not limited to antibody 6B4 and fragments thereof. Indeed, antibodies which bind to GP1b are known in the art and have been shown to bind GP1b *in vivo* and reduce platelet agglutination. Similarly, the production of monovalent fragments of antibodies was a technique which was commonly used at the time of filing and the variation of amino acids in the variable domains of antibodies and the effect thereof on the binding of the antibody or fragment to the antigen had no doubt been investigated for other antibodies prior to the filing of the present application.

The invention however relates, for example, to the use of monovalent fragments of monovalent GP1b-binding antibody fragments as pharmaceutical compositions based on

the observation that such fragments have the same inhibitory effect as complete antibodies on platelet aggregation without causing thrombocytopenia when administered *in vivo*. Thus, it is submitted that the skilled person based on the guidance provided in the description and the common general knowledge of antibody production and engineering, would have sufficient guidance to produce the antibody fragments and pharmaceutical compositions as presently claimed.

With respect to the Office's questioning the specification's enablement of the claimed pharmaceutical compositions, Applicants submit that this basis for the § 112 rejection — while cast in enablement terms — is, in reality, a utility rejection and should be properly evaluated under the Utility Examination Guidelines published in the Federal Register in July 1995 and now cited in the MPEP at § 706.03(a) and §§ 2107-2107.02. These Guidelines and the accompanying Legal Analysis apply to rejections based upon lack of utility, whether cited under 35 U.S.C § 101 or under § 112, first paragraph, as in the present case. The standard is whether the efficacy of a therapeutic is believable to those skilled in the art. Applying this standard to the present case, the § 112 rejection should clearly be withdrawn.

Moreover, as noted in the Guidelines, to uphold this ground for the § 112 rejection, the Examiner must establish the present case as one of those rare instances which meets the stringent criteria for rejection described in the Legal Analysis, i.e., "totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), as cited in the Legal Analysis, page 2, lines 44-45. According to the Legal Analysis, the only instances in which the Federal courts have found a lack of patentable utility was where, "based upon the factual record of the case, it was clear that the invention could and did not work as the inventor claimed it did." (Legal Analysis page 3, lines 10-12). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law

of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." (Legal Analysis page 9, lines 10-16).

Clearly, no such evidence is present in this case, and the use of Applicants' claimed compositions has not been shown to violate a scientific principle or law of nature. Applicants' specification provides clear and convincing evidence that the claimed antibodies bind to GP1b without causing thrompocytopenia in both a baboon and rat model systems. In short, Applicants note that no evidence is present in this case to doubt the objective truth of the statements found in Applicants' specification. Moreover, Applicants' specification does indeed demonstrate how the claimed pharmaceutical compositions are to be used, and presents compelling data demonstrating the *in vivo* efficacy of the claimed compositions. Accordingly, Applicants request reconsideration and withdrawal of this basis for the enablement rejection.

Written Description – Claims 65-79

Claims 65-79 were rejected under 35 U.S.C. § 112, first paragraph as for lack of a written description. For the following reasons, this rejection should be withdrawn.

Applicants submit that, to satisfy the written description requirement, one need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. The M.P.E.P. (§ 2163.02) states:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she has invented what is claimed."

To satisfy this standard, the Federal Circuit has held that the specification need only convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991).

Applicants' specification plainly meets this standard by providing a working

example of a monovalent antibody fragment which binds *in vivo* to GP1b. Moreover, Applicants have, from the time they filed this application, claimed this type of antibody as part of their invention. One skilled in the art would therefore certainly recognize that, at the time of filing, the inventors were in possession of claimed composition (claim 65) or monovalent antibody fragments (claim 75). The written description requirement of § 112, first paragraph has been satisfied by Applicants, and this rejection under § 112, first paragraph, should be withdrawn.

Moreover, the present specification would certainly indicate to one of ordinary skill in the art that Applicants discovered a "pharmaceutical composition comprising a monovalent antibody fragment which binds *in vivo* to human platelet glycoprotein GP1b without incurring thrompocytopenia and a pharmaceutically acceptable carrier." For example, Applicants' specification, at pages 12-13 describes such a pharmaceutical composition. Based on this description and other statements contained within the specification, one skilled in the art, would recognize and appreciate that Applicants had indeed invented the scope and content of the presently claimed invention.

In addition, Applicants point out that, with respect to claims 71 and 75, there can be no question that the written description requirement is satisfied, as a monovalent antibody produced from the cell line deposited with the Belgium Coordinated Collections of Microorganisms is described, for example, at page 13, Example 1.

In addition, with respect to amended claim 70 and new claim 83, there is no question that Applicants' specification provides a clear written description of the claimed subject matter. As stated in the Written Description Guidelines (66 FR 1106),

> [f]actors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from

> other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claimed monovalent antibody fragments are distinguished from other antibodies by both the structural characteristic of having at least 80% sequence identity to specific CDRs and by the specific functional characteristic of binding to GP1b. Additionally, Applicants note that the specification teaches other functional characteristics of the claimed antibodies, such as preventing the binding of von Willebrand factor to human platelet glycoprotein GP1b. Based on Applicants' disclosure of these properties and routine assays for determining whether a particular monovalent antibody fragment has these properties, one skilled in the art would appreciate that Appellants were in possession of the claimed invention. As clear distinguishing characteristics that are shared by the claimed antibodies are disclosed in Applicants' specification, this rejection should be withdrawn.

Thus, there can be no question that Applicants were in possession of the claimed genus at the time their application was filed, and that one skilled in the art would recognize Applicants' disclosure as a description of the invention defined by the present claims. As a result, Applicants' specification clearly satisfies the written description requirement, as set forth by the case law, and Applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 65-70, 72-74, and 76-79 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,455,030. Specifically, the Examiner states that the "[claim] limitations [i.e., "binds in vivo to human platelet glycoprotein GP1b without incurring thrombocytopenia"] are considered inherent properties." This rejection is respectfully traversed.

"[A]nticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citing *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999); and *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994)). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient." *Finnigan Corp. v. ITC,* 51 USPQ2d 1001 (Fed. Cir. 1999) *(*quoting *Continental Can Co., U.S.A. v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed Cir. 1991). "Anticipation, put simply, requires that every element of the claimed invention was previously 'described in a single reference.'" *Advanced Display*, 212 F.3d at 1283 (quoting *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991)). As is discussed below, the Office has not met this standard.

The '030 patent fails to disclose, either explicitly or inherently, an antibody that binds to GP1a, much less antibodies that bind to GP1b and prevent binding of von Willebrand factor. In fact, the '030 patent never even discusses using antibodies as pharmaceutical compositions for preventing and treating haemostasis disorders. The shortcoming of the '030 patent reference is that it does not expressly disclose the use of monovalent antibody fragments that bind to GP1b, a clear limitation of the claims.

The mere possibility that an antibody described in the '030 patent reference might be understood by one of skill in the art to bind to GP1b is insufficient to show that it is inherently disclosed in the reference. Moreover, the observation that the antibody of the prior art has a sequence homology of 83% at the amino acid level with the heavy chain

variable region of an antibody falling with the scope of Applicants in no way anticipates the claimed invention or suggests that the antibody of the prior art binds to GP1b. To the contrary, the skilled person would not consider that a monoclonal antibody, selected for its binding affinity to Bovine Growth Hormone, a protein which is structurally very different from GP1b, would cross-react with or bind to GP1b. Furthermore, the Office has provided no evidence supporting its contention that the functionally defined limitation of the antibodies as claimed is an inherent characteristic of any teaching found in the '030 patent reference. There is simply no basis in fact or technical reasoning to reasonably support that antibodies of the '030 patent, which are raised against antigens other than GP1b, would bind to GP1b. Because one skilled in the art would not necessarily recognize that the antibodies described in the '030 patent would bind to GP1b, it is not clear and convincing that the '030 patent reference inherently anticipates Applicants' claimed invention. Accordingly, Applicants respectfully request withdrawal of the § 102 rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 65-70, 72-74, and 76-79 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ward et al. (1995) in view of Owens et al. (1994) and U.S. Patent No. 4,731,245 (the '245 patent"). For the following reasons, Applicants respectfully traverse this rejection.

In characterizing the Ward reference, the Office states:

> Ward *et al* teach 17 monoclonal antibodies that bind GPIbα epitope of the platelet surface glycoprotein (see table 1 in particular). Ward et al teach that eight antibodies mapped to the N-terminal fragments of gplba, and these were tested for their ability to block binding of 125I-labelled von Willebrand factor to washed platelets in the presence of ristocetin or botrocetin. Ward et al teach that mAb P0 14 (epitope 1-282), P024 (epitope 1-282), P073 (epitope 1-282). P074 (epitope 1-282) and P077 (epitope 1-282 completely inhibited vWF

> binding with wither modulator (see page 1337, 1st col., 3rd paragraph and table 1 in particular). Finally, Ward et al teach that the inhibitory functions of the CD42b antibodies with their epitopes on gplba may provide valuable insights into mechanisms of vWF function both in vitro and in vivo (pg 1337, last paragraph in particular).

The Office further found that Owens teaches:

> Owens *et al* teach the modification of murine antibodies such as single chain antibody, a Fab fragment or a humanized antibody using monoclonal antibody technology. Owens *et al* further teach humanized antibodies use I therapy of human diseases or disorders, since human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications (see the entire document).

In addition, the Office, in connection with the '245 patent, states:

> The '245 patent teaches a composition comprising the antibody to the PLS antigen, as the active ingredient in association with a pharmaceutically acceptable carrier or excipient. The composition may preferably take the forms suitable for oral administration. Advantageously, the composition may be formulated in dosage unit form. The amount of the active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose (see col., 7 line 63 through col., 8 line 3 in particular).

Based on these references, the Office concluded that "the invention taken as a whole is *prima facie* obvious over the prior art." In reaching this conclusion, the Office explained:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Ward et al as Fab as taught by the Owens *et al* and place the resultant Fab fragment which binds to platelet glycoprotein GPIbα polypeptide taught by the Ward et al reference in a composition taught by the '245 patent.

> One of ordinary skill in the art at the time the invention was made would have been motivated to do so because eight antibodies mapped to the N-terminal fragments of gpIba, and these were tested for their ability to block binding of ^{125}I-labelled von Willebrand factor to washed platelets in the presence of ristocetin or botrocetin and because it would further lead to insights into mechanisms of vWF function both in vitro and in vivo. Given that the antibody fragments are the reagents of choice for some clinical applications one ordinary skill I the art at the time the invention was mad would be motivated to include such fragments in a composition because the composition can be formulated in dosage unit form. The amount of the active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose as taught by '245 patent.

Applicants' application in general includes claims directed to (1) a pharmaceutical composition and (2) a monovalent antibody. Independent claims 65 and 72 are representative:

> 65. A pharmaceutical composition comprising a monovalent antibody fragment which binds *in vivo* to human platelet glycoprotein GPIb without incurring thrombocytopenia and a pharmaceutically acceptable carrier.
>
> 72. A monovalent antibody fragment which binds *in vivo* to human platelet glycoprotein GPIb, and prevents the binding of von Willebrand factor to human platelet glycoprotein GPIb.

In determining whether an invention is obvious, the Office must determine if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. The factual inquiries underlying obviousness include (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue,

(3) the level of ordinary skill in the art at the time the invention was made, and (4) any objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966). "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Obviousness requires one of ordinary skill in the art have a reasonable expectation of success as to the invention--"obvious to try" and "absolute predictability" are incorrect standards. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

The Federal Circuit has further stated:

> "[V]irtually all [inventions] are combinations of old elements." Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998) (internal citations omitted).

Moreover, the court has explained that "[t]o prevent the use of hindsight based on the invention to defeat patentability of the invention, ... the examiner [is required] to show a motivation to combine the references that create the case of obviousness." *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). Simply put, in order to establish a *prima facie* case of obviousness, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art

references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). As explained below, the Office has failed to show a *prima facie* case of obviousness and the rejection should be withdrawn.

As motivation for combining the cited references, the Office states that "because eight antibodies mapped to the N-terminal fragments of gp1ba and because it would lead to insights into the mechanisms of vWF function." There is, however, nothing in the references of record that provides any basis for selecting a monovalent antibody fragment that binds to GP1b as claimed, and the Office's analysis amounts to merely an invitation to experiment.

First, the Office's statement that "[g]iven that the antibody fragments are reagents of choice for some clinical applications one [of skill in the art] would be motivated to include such fragments in a composition," is plainly predicated on an improper "obvious to try" standard. It is insufficient that one skilled in the art might find it "obvious to try" combining the Ward, Owens, and '245 patent references. As the Federal Circuit has held, an obvious to try situation does not render a claim "obvious" within the meaning of section 103. ("An invention is obvious to try rather than obvious within the meaning of § 103 ""where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful."" *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).)

It is undisputed that neither Ward, Owens, nor the '245 patent contains an express suggestion that either a " a monovalent antibody fragment which binds to ... GP1b," much less a "pharmaceutical composition comprising a monovalent antibody fragment which binds to ... GP1b." Moreover, nothing in the cited references would have suggested to a person of ordinary skill in the art that a monovalent antibody would function *in vivo* without incurring thromocytopenia as claimed. The Office, apart from pointing out that Ward teaches 17 monoclonal antibodies that bind GP1bα epitope,

provides no scientific evidence or reasoning that there would have been a "reasonable expectation of success" in creating a functional monovalent antibody fragment.

The Examiner has referred to Ward as disclosing antibodies that bind GPIbα epitope. On the contrary, Ward relates to intact monoclonal antibodies which are shown to inhibit wWF binding and ristocetin and botrocetin-induced platelet aggregation *in vitro*. Ward et al. speculates that "further studies comparing inhibitory functions may provide valuable insights into the mechanisms of wWF function *in vitro* and *in vivo*" (emphasis added), but provides no *in vivo* data. It is clear that Ward was only beginning to investigate GP1b antibodies. Indeed, Ward's antibodies were developed to perform epitope-mapping *in vitro*. Although these data may help to explain how proteins interact *in vivo*, they are not necessarily useful as pharmaceutical compositions. This reference provides no scientific or logical predicate for rendering Applicants' claims obvious.

Second, Ward carried out *in vitro* experiments, which, as is well known, frequently fail to be predictive of *in vivo* results. Claim 65 requires that the monovalent antibody bind *in vivo* ... without incurring thrombocytopenia. Claim 72 requires a monovalent antibody which binds *in vivo* to GP1b and prevents the binding of von Willebrand factor to GP1b. Ward fails to teach a single monovalent antibody to GP1b, much less one that binds *in vivo* to von Willebrand factor. Moreover, nothing in the Ward *in vitro* experiments takes into account whether thrombocytopenia is prevented *in vivo*.

Furthermore, Applicants note that a number of anti-GP1b antibodies had been described in the art at the time of filing of the present application. Despite their ability to block ristocetin-induced platelet aggregation *in vivo*, these antibodies would not be considered as suitable pharmaceutical compounds by the skilled person as these antibodies were also found to induce thrombocytopenia when used *in vivo*. As evidence of this assertion, Applicants direct the Examiner's attention to the publication of Cadroy *et al.*, *Blood* 83:3218-3224 (1994) and Bergmeier *et al.*, *Blood* 95:886-893 (2000) (a copy of each reference is provided in the accompanying information disclosure statement),

which both describe the administration of monoclonal antibodies to GP1b or F(ab)2 fragments thereof *in vivo* in animal models. In contrast to Applicants' claimed invention, both articles report the immediate induction of thrombocytopenia upon administration of the antibody.

Turning now to Owens, this reference describes the modification and production of antibodies or fragments by genetic engineering. Different types of antibodies and fragments are discussed. Generally, problems encountered with natural antibodies are described. In the context of the construction of Fv and single chain Fv fragments, the advantage of Fvs over Fab antibodies is presented. Owens does not specifically describe the advantages of monovalent antibody fragments (Fabs or Fvs) over complete antibodies or F(Ab)2 fragments. Given this teaching, Owens plainly does not suggest Applicants' claimed invention. Accordingly, Owens cannot teach or suggest what they themselves did not know or recognize. The Ward and Owens references are unavailing, and, in combination, cannot support the present obviousness rejection.

The '245 patent is cited for teaching a composition that includes antibody as an active ingredient. It provides no information regarding Applicants' claimed invention either alone or in combination with Ward or Owens.

With respect to claim 65, Applicants again note the invention relates to the use of monovalent GP16 antibody fragments as pharmaceutical compositions because it is based on Applicants' discovery that monovalent antibody fragments are capable of inhibiting platelet aggregation (which is required for an anti-thrombotic effect) without causing thrombocytopenia. Furthermore, as indicated above, the skilled person at the time of filing of the present application was aware of the thrombocytopenia induced by antibodies against GP1b based on the publications describing *in vivo* experiments in animal models, and therefore would not be motivated to use such antibodies as pharmaceutical compositions. Applicants further note that there is no indication in the art as to what caused this thrombocytopenic side-effect. Accordingly, Applicants submit that it was

unobvious for the skilled person to develop a monovalent antibody fragment that binds to GP1b as a pharmaceutical at the time of filing.

Finally, the Office has failed to explain, when analyzing the references made of record, what specific understanding would have suggested the combination of references relied on by the Office, especially in view of the Applicants' results. Instead, the obviousness analysis in the Office Action is limited to a discussion of how the references can be pieced together to yield the claimed invention. As the Federal Circuit stated in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985):

> It is an error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a "blueprint." When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself.

To believe that one skilled in the art would be motivated to generate Applicants' disclosed monovalent antibody fragments, when Ward, Owens, and the '245 patent, either alone or in combination, never even discuss, suggest, or mention instructions for making the claimed antibodies is to assume a level of inspiration constituting inventive activity. The case law makes clear that to avoid a hindsight-based obviousness analysis that the Patent Office bears the burden of elucidating factual teachings, suggestions, or incentives from the prior art that show the suitability of the combination of references. *See Graham v. John Deere Co.*, 383 U.S. 1, 18, 148 U.S.P.Q. 459, 467 (1966) ("strict observance" of factual predicates to obviousness conclusion required). For all of the above-mentioned reasons, this burden has not been met and the rejection of the claims under § 103(a) for obviousness over these references should therefore be withdrawn.

In conclusion, the Office's finding of obviousness is neither supported by a scientifically reasoned basis, nor substantial evidence. The Office has not shown a proper *prima facie* case of obviousness, and the rejection of the claims under § 103 for

obviousness over Ward in view of Owens and the '245 patent should therefore be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to telephone the undersigned at the number below if doing so would be helpful to resolve any outstanding issues.

Enclosed are a Petition to extend the period for replying to the Office Action for one (1) months, to and including March 4, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 4 March 2005

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